REMARKS

In the amended claims enclosed herewith, claim 1 has been amended by the introduction of the limitation that after the concentration step the pharmaceutical formulation is filled directly into sterile recipients ready for pharmaceutical use, or sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use. Basis for this amendment is found in previous claim 2 and on page 12, paragraph 4, of the application as filed. Previous claim 2 is now cancelled without prejudice, (the right to file a divisional or continuation application is reserved). Finally, claim 4 has been amended to depend correctly from claim 1, and term "acing" has been corrected to "according" as requested by the Examiner. The Examiner's claim objections to claim 4 are accordingly rendered moot.

Concerning the Examiner's rejection of the pending claims on ground of double-patenting or obviousness under 35 USC § 112 second paragraph, please consider the following.

The present invention as claimed in amended claim 1 is directed to a process for preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration, comprising the steps of providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration; passing said aqueous formulation through a filter having a pore size less than 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling of water until said specified concentration is reached; and after the concentration step filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use.

In addition to the arguments filed in response to the first Office Action, the following is also highlighted.

WO 00/44925 teaches a process for the preparation of a purified HA powder, involving steps of diafiltration and removing of cells from an aqueous solution of hyaluronic acid obtained from a biological source, followed by sterilizing the dilute HA containing solution by passing through a 0.2μm filter and freeze drying the solution to obtain a dry powder of purified HA. The process taught by WO 00/44925 produces a sterilised purified dry powder of HA and not an aqueous sterile pharmaceutical formulation of HA ready for pharmaceutical use. Accordingly it is clearly seen that WO 00/44925 specifically teaches away from the preparation of a sterile ready-to-use aqueous pharmaceutical formulation filled directly from the concentration step either into sterile recipients, or into sterile tanks and subsequently directly into sterile recipients, ready for pharmaceutical use according to the process of the present invention as claimed. Indeed WO 00/44925 specifically teaches the preparation of a dry purified sodium hyaluronate powder, and that once obtained, this dry HA powder may in a subsequent step be "used for preparing pharmaceutical compositions" (see for instance WO 00/44925 page 14 second paragraph, and page 16 second paragraph).

Before the concentrated HA powder product of the process of WO 00/44925 can be used for pharmaceutical applications it must be prepared into a ready-to-use pharmaceutical formulation in the conventional manner. That is to say by weighing out accurately a specific amount of the sterilised concentrated sodium hyaluronate powder, mixing this powder with a defined precise volume of water and precise quantities of excipients, in order to get the required accurate concentration of HA in the aqueous formulation necessary for pharmaceutical use. The thus prepared HA containing aqueous formulation may then be filled into vials and syringes

ready for pharmaceutical use. This weighing and mixing of the sterilised HA powder necessary for the preparation of an aqueous pharmaceutical formulation necessarily requires the removal of the sterilised HA powder from its storage vessel, transfer to a measuring vessel, and then to a vessel in which the powder will be mixed with water; thereby introducing, at each manipulation, a risk of contamination. In order to meet health authority standards for administration in the human body the thus prepared aqueous formulation must be subjected to further sterilisation, such as by autoclaving of the solution filled in vials or syringes.

The process of the present invention as claimed in claim 1 avoids all of the above-mentioned problems. Moreover, the process of the present invention allows the preparation of a ready-to-use sterile pharmaceutical formulation of HA in which the required properties of high molecular weight of the hyaluronic acid and determined high viscosity are maintained. No additional preparation steps are required before pharmaceutical use of the HA formulation prepared according to the process of the present invention. Since the pharmaceutical formulation is filled directly from the process into sterile tanks or sterile recipients, e.g., vials or syringes, avoids the risks of contamination due to transport, weighing and mixing separate sterile components as in prior art methods. Further the process of the present invention avoids the need to measure accurate quantities of hyaluronic acid powder and precise volumes water to be mixed in order to obtain a specified accurate concentration of hyaluronic acid in the aqueous formulation, and further avoids the need of any measures for ensuring that the specified concentration is maintained during the sterilisation process, since the concentration of the formulation is accurately monitored to arrive at the requisite concentration during the vacuum concentration step (see for example page 7 paragraph 1, and page 11 paragraph 4, and of the present application as filed).

With respect to the document EP 0 631 799 , in addition to the arguments previously presented, it may be highlighted that although the use of vacuum concentration for the concentration of aqueous solutions is a known technique, EP 0 631 799 does not provide any teaching whatsoever of the preparation of a sterile ready-to-use pharmaceutical formulation having a pre-determined specified accurate concentration of hyaluronic acid, filled directly into sterile recipients (such as syringes and vials) ready for pharmaceutical use, or into storage tanks and subsequently directly into sterile recipients ready for pharmaceutical use according to the process of the present invention.

EP 0 631 799 is directed to a vacuum concentrating plant which uses a heat pump with the aim of providing high heating efficiency. It is noted that EP 0 631 799 is not concerned in any way with the preparation of sterile pharmaceutical formulations having an accurate, pre-determined, concentration necessary for medical applications. EP 0 631 799 does not describe or suggest any means that would allow the monitoring of the concentration of the liquid in the vacuum evaporator during the concentration process, nor any means for stopping the vacuum evaporation concentration process abruptly when the desired concentration of substrate has been reached, so as to be able to provide an aqueous solution of hyaluronic acid salt having a specific concentration, within a very narrow limit of variations, required for medical use. Moreover there is no teaching whatsoever in EP 0 631 799 of the functioning of the vacuum concentration plant described therein for providing a sterile product as required for pharmaceutical use.

It may further be highlighted that the invention as claimed is not the use of evaporation under vacuum to concentrate a solution comprising hyaluronic acid, but on the contrary lies in the provision of a process preparing a sterile ready-to-use aqueous pharmaceutical formulation comprising a high molecular weight hyaluronic acid salt (HA) at a specified concentration

involving the specific combination of the steps of; providing an aqueous formulation comprising high molecular weight HA at a concentration of less than the specified concentration; passing said aqueous formulation through a filter having a pore size less than 0.45 μm and greater than 0.1 μm; concentrating said aqueous formulation by applying a vacuum and boiling of water until the requisite accurate concentration is reached; and after the concentration step filling the pharmaceutical formulation directly into sterile recipients ready for pharmaceutical use, or into sterile tanks and subsequently directly into sterile recipients ready for pharmaceutical use.

For all of the foregoing reasons, Applicant respectfully requests entry of the foregoing amendments, reconsideration of the present application in light thereof, and an allowance of all claims now pending over all the prior art of record.

Respectfully submitted,

By: _____

Clifford W. Browning
Reg. No. 32,201
Krieg DeVault LLP
One Indiana Square
Suite 2800
Indianapolis, IN 46204
(317) 238-6203